GAU 1654

Patent Application
Attorney Docket No.PC7981C

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By _____
(Signature of person mailing)

Evelyn Sabatino
(Typed or printed name of person)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: John A. Lowe :

Examiner:Cybille Delacroix-Muirheid

APPLICATION NO.:09/007,268 :

Group Art Unit:1654

FILING DATE:January 14, 1998 :

TITLE: Fluoroalkoxybenzylamino Derivatives of Nitrogen Containing Heterocycles :

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Communication and Amendment

In connection with Applicant's review of the pending Official Action, it was determined that the Patent Office copy of the Specification herein may be missing Page 41. The missing text is identical to text of PCT/US92/03571 which, at entry into the U.S. national stage, became Serial No. 08/167,881. The present application is a divisional of the '881 application. Since there has been a continuous chain of co-pendency, entry of the text, if determined to be missing, is appropriate.

Amendment

Please insert the attached page (numbered as page 41), into the Specification as page 41.

Respectfully submitted,

Date: 12/20/99

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and washed with ether to obtain 600 mg of the title compound, m.p. > 250°C.

^{1}H NMR (free base, $CDCl_3$) δ 1.36 (s, 1H), 1.54 (m, 1H), 1.86 (m, 1H), 2.06 (m, 1H), 2.76 (m, 2H), 3.22 (m, 1H), 3.32 (d, 1H, J=15), 3.48 (s, 3H), 3.58 (d, 1H, J=15), 3.85 (d, 1H, J=3), 6.57 (d, 1H, J=9), 6.80 (d, 1H, J=3), 6.92 (dd, 1H, J=3, 9), 7.22 (m, 5H).

HRMS Calc'd for $C_{20}H_{23}F_3N_2O_2$: 380.1711. Found: 380.1704.

Anal. Calc'd for $C_{20}H_{23}F_3N_2O_2 \cdot 2HCl \cdot 0.2H_2O$: C 52.57, H 5.60, N 6.13. Found: C 52.58, H 5.40, N 5.97.

EXAMPLE 5

(2S,3S)-1-(5,6-Dimethoxyhexyl)-3-(2-methoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine hydrochloride

Under a nitrogen atmosphere in a round-bottom flask were placed 250 mg (0.66 mmol) of (2S, 3S)-3-(2-methoxy-5-trifluoromethoxybenzyl)amino-2-phenylpiperidine, 2 mL of tetrahydrofuran (THF) and 0.28 mL (2.0 mmol) of triethylamine. To the system were added 475 mg (2.0 mmol) of 5,6-dimethoxy-1-methylsulfonyloxyhexane (prepared from 1,5,6-hexanetriol by sequential acetonide formation (acetone, p-toluenesulfonic acid), acetylation (acetyl chloride, triethylamine, THF), acetonide cleavage (60% acetic acid/water), dimethylation (sodium hydride, methyl iodide, THF), deacetylation (sodium methoxide, methanol) and methanesulfonate ester formation (methanesulfonyl chloride, triethylamine, THF)), and the mixture was heated at 50-60°C for four days. The reaction mixture was partitioned between $CHCl_3$ and saturated aqueous sodium bicarbonate and extracted with three portions of $CHCl_3$. The combined organic fractions were dried (Na_2SO_4), filtered and concentrated to obtain 853 mg of an orange oil. The crude material was purified by flash column chromatography (35 g of silica gel) using 1:19 methanol/chloroform as the eluant to obtain 185 mg of yellow oil. Th oil was diss lved in ethyl acetate and ether saturated with HCl was added t the s lution. The mixture